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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/12/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed December 12, 2005. Applicant's response to restriction requirement of November 3, 2005 has been entered. No claims were amended or withdrawn. Currently, claims 1-21 are pending in the application.

Election/Restrictions

Applicant's election of Group I (claim 1-11), with traverse, drawn to a method producing cardiomyocytes and for improving ventricular wall motion in a heart of an individual, comprising administration of cardiomyocyte producing mesenchymal stem cells (MSCs), is acknowledged. Claims 12-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the Paper filed December 12, 2005. Because Applicant did not distinctly and specifically point out the supposed errors in the examiner's action, the requirement for restriction is maintained and hereby made FINAL.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-2 and 4-10 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method producing cardiomyocytes in a heart of an individual, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs, does not reasonably provide an enablement for a method of administering said MSCs from any source, including xenogeneic, or MSCs that are genetically modified, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claim 1 is drawn to a method producing cardiomyocytes in a heart of an individual, comprising: administering intravenously to said individual a cardiomyocyte producing amount of MSCs. Claims 2 further limits the dose of MSCs administered. Claim 4 is drawn to a method of improving wall motion of the heart of an individual, comprising administering to said individual a cardiomyocyte producing amount of MSCs. Claims 5-10 further limit claim 4 to routes of administration and administration during open surgical procedure. When given their broadest reasonable interpretation, in view of the as filed specification, claims 1-2 and 4-10 encompass methods of administering said MSCs from any source, including cells that are xenogeneic in origin. The specification teaches that the MSCs may be genetically modified or engineered to contain genes which express proteins of importance for differentiation and/or maintenance of striated muscle cells (line 15-17, p. 4). The specification additionally envisions the use of MSCs "in accordance with the invention, in order of preference, autologous, allogeneic or xenogeneic (lines 15-16, p. 8).

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to produce cardiomyocytes in a heart of an individual or improve ventricular wall motion, as claimed in claims 1-2, and 4-10 of the instant application.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art with regard to transplantation of MSCs and gene therapy are effectively summarized by the references of Prockop (Science 276:71-74, 1997; of record); Gerson, S. (Nature Medicine 5:262-264, 1999; of record); Saadi et al. (Life Sciences 62:365-387, 1998); and Verma et al. (Nature 389:239-242, 1997, of record).

The prior art at the time of filing suggests that MSC transplantation and *in vivo* therapeutic effectiveness have not been established such that utilizing these cells to treat diseases, disorders, or conditions is routine or predictable. For example, Prockop indicates that several different strategies are being pursued for therapeutic use of MSCs and notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy" (p. 74, center column). Similarly, Gerson indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens (p. 264, left column). Thus, while the teachings indicate that mesenchymal or marrow stromal based therapies appear to be promising, the specific methodologies and clinical efficacy of such therapies remain to be established.

Additionally, transplantation of MSCs in the examples given utilizes autologous or allogeneic sources for the stem cells, as it is well recognized in the art that transplant of xenogeneic cells to a recipient induces a severe immune response, resulting in subsequent loss of transplanted tissue. Saad et al. teach that success of xenotransplantation is confounded by tissue rejection caused by host immune responses. Various factors need to be considered for xenotransplantation, including selection of a donor species and the transplant's compatibility with the recipient, which could induce cellular or humoral rejection (Figure 1, p. 367). Furthermore, they conclude: "thus, it is not possible to predict that xenotransplantation will enter the clinical arena in a very few years (p. 381).

Moreover, at the time of filing, the art of gene therapy was known to be unpredictable and non-routine. Verma et al. indicate that "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged; problems such as lack of efficient delivery systems, lack of sustained expression, and host

immune response reactions remain formidable challenges; although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story: (p. 239, under Abstract, and left column, paragraphs 1-2).

In view of the lack of teachings or guidance provided by the specification with regard to genetic modification of MSCs and use in gene therapy, and the lack of teachings or guidance provided by the specification to overcome the difficulties and unpredictability of xenogeneic MSC transplantation, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of MSCs that are genetically modified or engineered to contain genes which express proteins of importance for the differentiation and/or maintenance of striated muscle cells (as envisioned on p. 4, lines 15-18 of the instant specification); or the production of MSCs from a xenogeneic source (as stated in line 15, p. 8 of the instant specification). The specification discloses allogeneic MSCs used for transplantation in pig (Examples 4 and 5, p. 15 and 18; and Fig. 3). The specification further describes the implantation of human MSCs into athymic rat myocardial tissue (Example 1, pp. 10-11). However, athymic rats lack the ability to mount an immune response against xenogeneic MSCs. Therefore, Example 1 does not represent a true xenogeneic transplant ot MSCs to cardiac tissue.

The specification provides no additional examples of xenografts or transfer of genetically modified MSCs. The specification does not provide the guidance required to overcome the art-recognized unpredictability of transplant of genetically modified MSCs or xenografts.The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the production of cardiomyocytes by autologous or allogeneic MSCs following transfer of said MSCs to cardiac tissue.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of the method of administering MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to produce cardiomyocytes in a heart of an individual or improve ventricular wall motion, as claimed in claims 1-2, and 4-10 of the instant application. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Summary

Applicant is therefore enabled for a method producing cardiomyocytes in a heart of an individual, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs that are not genetically altered. In the instant case, as discussed above, in a highly unpredictable art where the transplantation of xenogeneic MSCs will likely produce a severe immune response and likely lead to tissue rejection, and the lack of knowledge of whether cell and gene therapy is effective in treatment regimens, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,387,369. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the instant application embraces a method for producing cardiomyocytes in a heart of an individual in need thereof, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells in at least 20μl and up to about 150 ml of a suspension containing 10-40x10^6 mesenchymal cells/ml. Claim 1 of the 369 patent is directed to a process for producing cardiac muscle cells in the heart of an individual in need thereof, comprising: administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to produce cardiac muscle cells in the heart of said individual, said administered mesenchymal stem cells differentiating into cardiac muscle cells thereby producing cardiac muscle cells in the heart of said individual. The cardiomyocytes of claim 1 of the instant application are synonymous to the cardiac muscle cells of the 369 patent and also embrace autologous or allogeneic mesenchymal stem cells. Further, the specification of the 369 patent states: "multiple injections of 20-50 μl (10-40x10^6 MSCs/ml) are envisioned. Follow-up therapy may involve additional dosings. In very severe cases, e.g. in a range around the 40% tissue involvement severity level, multiple equivalent doses for a more extended duration with long term (up to several months) maintenance dose aftercare may well be indicated" (third and fourth paragraphs, column 5). As no upper limit for the volume of stem cells is indicated, a volume of up to about 150 ml may be envisioned, as can the

range of 40 ml to 150 ml of claim 2 in the instant application. Claims 3 and 11 are directed to allogenic mesenchymal stem cells, described in claim 1 of the 369 patent.

Claim 4 is directed to improving ventricular wall motion of the heart of an individual. Claim 2 of the 369 patent is drawn to regenerating or repair of cardiac muscle of an individual that has been damaged through disease. Claim 11 of the 369 patent is directed to a process of reducing scar formation in infracted heart tissue. Taken together, claims 2 and 11 of the 369 patent would result in improving ventricular wall motion. This is demonstrated in post-filing art, where transplantation of autologous unmanipulated bone marrow containing MSCs into scarred myocardium of infarcted patients was shown to enhance cardiac function (Galinanes et al., Cell Transplantation 13:7-13; 2004; Title). Galinanes et al. show that following unmanipulated bone marrow stem cell transplantation into damaged myocardium of patients, "only the left ventricle segmental wall motion score of the areas injected with bone marrow and receiving a bypass graft in combination improved" (Abstract).

Claim 5 is directed to direct administration of autologous or allogeneic mesenchymal stem cells to at least one damaged portion of heart tissue. Claim 4 of the 369 patent involves the process of regenerating cardiac muscle that has been damaged through disease, by directly administering mesenchymal stem cells to the heart.

Claim 6 further limits claim 5 to administration by injection, that is also the limitation of claim 6 of the 369 patent.

The limitation of claim 7 involves the administration of autologous or allogeneic mesenchymal stem cells in a pharmaceutically accepatable liquid injectable carrier. To practice the invention of the 369 patent commensurate with the scope of claims 1-10, it would have been obvious to utilize a pharmaceutically acceptable liquid injectable carrier to administer stem cells by injection in a pharmaceutically acceptable carrier, wherein the subject is human (claim7 of the 369 patent).

Claim 8 is drawn to the direct administration of the autologous or allogeneic mesenchymal stem cells during an open surgical procedure. The specification of the 369 patent describes: "under sterile conditions, a 20 mm anterior thoracotomy was performed, and following visualization of the left ventricle, 10 μl of the cell suspension, containing 10,000 to 100,000 MSCs in serum-free medium were injected into the left ventricular apex" (lines 28-33, column 6). The limitation of administration by injection is further covered for claim 9 of the instant application.

Claim 10 is directed to intravenous administration of autologous or allogeneic mesenchymal stem cells to improve ventricular wall motion. Claim 5 of the 369 patent describes systemic administration that encompasses intravenous administration. Furthermore, given that depending on an intended individual subjected to the treatment, e.g., weight, the severity of a need to cardiomycytes, route of administration, it would have been obvious to one of ordinary skill in the art as a matter of design choice or suitability to employ a suitable volume containing a suspenstion containing a sufficient amount of allogeneic or autologous mysenchymal stem cells to the individual, especially since the patent claims clearly claim that so long as an effective amount of aulogous or allogenic mesenchymal stem cells are employed, a desired amount of cardiomycytes shall be produced *in vivo*. Therefore, to practice the invention of the 369 patent, it would have been obvious to utilize the methods claimed in claims 1-11 of the instant application.

Conclusion

No claims allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

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Examiner, USPTO, AU 1633

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